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CLINICAL OPINION

Basic science and clinical aspects of mesh infection in pelvic floor reconstructive surgery

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Abstract
Introduction and hypothesis Bacterial colonization following mesh-augmented pelvic floor reconstructive surgery for pelvic organ prolapse is probably an underestimated consideration.
Methods Although clinical infections are rare, subclinical contamination of the polypropylene mesh has been systematically demonstrated by bacteriological analyses during mesh implantation and on explanted meshes.
Results A model of subclinical mesh infection does exist and bacterial colonization and mesh shrinkage have recently been correlated experimentally.
Conclusions New meshes with surface modifications or an antibiotic or antiseptic coating should be explored.

Keywords Polypropylene mesh · Vaginal surgery · Infection · Erosion · Shrinkage

Introduction

Non-absorbable polypropylene meshes are widely used for pelvic floor reconstructive surgery by the vaginal route. Although they provide appropriate support, their use is restricted by complications of poorly understood origin such as erosion, pain and shrinkage. Many factors have been suspected such as the characteristics of the polypropylene mesh (weight, pore size, stiffness and elasticity), surgical technique, surgeon experience and associated hysterectomy, but even when these factors are controlled, some patients still experience incomprehensible painful shrinkage. Several hypotheses may be put forward to explain this: firstly, an immune reaction to a foreign body [1], but this does not explain the relatively better tolerance of the same material by the abdominal route; secondly, a prolonged inflammatory response (oxidative attack), as previously shown in abdominal hernia [2] and thirdly, a chronic infection.

Our objective is to review the basic science and recent clinical aspects of mesh infection in pelvic floor reconstructive surgery.

Pathophysiology of mesh infection

In other surgical specialities, such as orthopaedics, where the number of patients requiring biomaterials implant surgery is steadily increasing, biomaterials-related infection is one of the main causes of implant failure [3]. In a very interesting paper published by Gristina in *Science* in 1987, it was admitted that one of the major barriers to the extended use of implanted devices is the possibility of bacterial adhesion to biomaterials through the highly adaptive ability of bacteria to colonize the surfaces of "inert" biomaterials or adjacent damaged tissue cells [4]. Biomaterial implantation is followed immediately by a "race for the surface", a contest between tissue cell integration and bacterial adhesion to that same surface. If

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the bacteria win, the surface is occupied and is thus less available for tissue integration. Furthermore, adhesion-mediated infections are notoriously resistant to antibiotics and host defences, and tend to persist until the biomaterial is removed.

In other words, microorganisms can interfere with the integration process through adhesion to mesh surfaces, and such adhesion is an important stage in the infection [5]. The first stage of adhesion is physical and reversible, but the second is molecular and irreversible [6]. And, it has been suggested that this second stage is dependent upon the adaptative mechanisms of the bacteria itself. A low density of bacteria can produce a protective polysaccharide "biofilm" (slime) that allows the bacteria to remain quiescent. These bacteria may then multiply following an intercurrent event, e.g. an alteration in host immune defences [5]. Chronic infections may therefore appear several months or even several years after mesh implantation [7]. This mechanism of chronic infection may also explain the low bacterial density usually found on explanted meshes [8].

Vaginal surgery is a "clean–contaminated surgery" since the vagina is naturally colonized by bacteria and is located close to the anus. Bacterial contamination may occur when the mesh is initially inserted through faulty asepsis in handling, prepping the vagina or because of the proximity of the anus [8]. Contamination may occur during vaginal closure, when vaginal flora comes in contact with the mesh.

Escherichia coli is common in vaginal infections and is one of the most frequent bacteria responsible for infected biomaterial [4]. Such bacteria on the mesh may also be explained by the conversion of typically non-pathogenic bacteria into virulent colonies adherent to the material [9].

Clinical evidence of mesh infection

Clinical data and experiments have shown that polypropylene is the synthetic material least susceptible to infection and that monofilament should be preferred to multifilament meshes [9]. A large contact area favours bacterial persistence and development in multifilament meshes. As the distance between the filaments is less than 10 μm, bacteria that are around 1 μm in diameter can colonize the mesh, but inflammatory cells (macrophages, neutrophils) are too big to enter [10]. And, whereas the macropores in polypropylene meshes allow inflammatory cells to reach the site of infection [11], microporous suburethral tapes were withdrawn from the market because of the many infectious complications reported [12]. However, even if the rate of clinical infection (periprosthetic abscess) with monofilament, large-pore polypropylene meshes is low (<1%), clinical evidence points to chronic infection occurring frequently.

In a prospective study of 64 consecutive patients undergoing vaginal implantation of a lightweight, collagen-coated monofilament polypropylene mesh, Vollebregt et al. [13] showed that 83.6% of the meshes were colonized by different types of bacteria. These results were obtained using culture swabs of the core mesh during surgery. The rate of bacterial colonization was high despite double disinfection of the surgical area with iodine, prophylactic antibiotic therapy with intravenous cephazolin and metronidazole, a separate drape covering the anal region, a change of gloves and instruments and mesh kept in its sterile pack as long as possible. The bacteria swabbed from the meshes were potentially pathogenic in 13.4% of cases (*Staphylococcus aureus*, *E. coli*, *Bacteroides*, *Enterococcus*, *Proteus mirabilis*), but were present at a very low density ($<10^3$ CFU/mL). Postoperatively, 4.7% of the women presented unexplained fever but none showed any signs of infection up to 6 months later.

The bacteriological analysis of 16 meshes removed because of complications following the surgical management of urinary incontinence or pelvic organ prolapse showed multimicrobial infection in 31% of cases, including *P. mirabilis* (in 25%), *E. coli*, *Staphylococcus*, *Streptococcus* and *Enterococcus* [8]. Bacterial contamination was found in all meshes, even in a case of repeat surgery for mesh shrinkage with no erosion. Bacterial density was low ($<10^3$ CFU/mL) in 43% of cases but in others reached 10^5 CFU/mL.

Another study reported by Marcus-Braun and von Theobald concerned the retrospective analysis of 83 patients who underwent 104 repeat operations mainly for complete or partial mesh removal [14]. The main indications for mesh removal consisted of erosion (n=44) and infection (n=30). Among infected cases, only five patients showed abscess (16.7%), and cultures were positive in only seven cases (23.3%), with *E. coli* and *S. aureus* as principal bacteria. In this study, repeat erosion was associated with underlying infection, and recurrent infection was resolved only by complete mesh removal. Furthermore, 66.6% of infections were detected more than 2 years, and some up to 4 years, after mesh implantation.

Clave et al. recently reported on an analysis of 84 meshes explanted for erosion (69%), infection (17%), or shrinkage or pain (14%) [15]. Histological examination revealed mainly two types of periprosthetic tissue reaction, including infection in 44% of cases (altered polymorphonuclear neutrophils) and chronic inflammation in 42% of cases (giant cells and mononuclear cells). A minor contamination process was suspected even in the second type because of the presence of unaltered polynuclear cells associated with partial mesh colonization. Monofilament polypropylene was less frequently associated with infection than multifilament and composite meshes (39% versus

70%, $p=0.02$). Clave et al. reported signs of polymer degradation with polypropylene, particularly in the case of infection (59% of cases).

Finally, several cases of chronic infection due to *Actinomyces israelii* have been reported, particularly in cases of recurrent vaginal erosion following TVT, bone anchored sling and sacrospinous ligament suspension [16–18]. The diagnosis of such an infection requires biopsies of eroded mesh and vaginal tissue around the erosion area for both histological examination and bacterial samples for aerobic and anaerobic culture.

Risk factors for mesh infection

Significant risk factors for mesh infection following ventral hernia repair consist of prolonged operative time [OR 1.38 (95%CI 1.2–1.6)], steroid use [OR 4.15 (95%CI 1.5–11.1)] and smoking [OR 2.46 (95%CI 1.3–4.6)] [19].

In vaginal surgery with mesh, age (>60 years old) and smoking (>6.85 pack years) are associated with vaginal erosion, with relative risks at 1.6 and 3, respectively [20]. Age is responsible for changes in the function of inflammatory cells, reduced extracellular matrix and impaired angiogenesis. Smoking is responsible for vasoconstriction, the formation of microthrombi, decreased fibrinolytic activity and direct endothelial injury. In the same study, smoking was also significantly associated with postoperative infection.

Although other factors such as poor vaginal tissue vascularity, inadequate vaginal tissue coverage and postoperative hematoma are probably also risk factors for infection, there is no evidence for this in the literature. Therefore, no recommendations (such as prolonged antibioprophylaxis, time to repeat operation) can be made for the management of postoperative hematoma around the mesh or for early mesh exposure.

Mesh infection in an animal model

We have previously described an animal model of mesh infection based on the well-known model of incisional abdominal hernia in Wistar rats. Here, the bacterial inoculate is injected immediately after mesh implantation and skin closure, and a bacterial analysis is performed 1 month later [21]. Such a model could be used to compare the in vivo bacterial infectivity of the different biomaterials used in vaginal surgery. But, such a model must be reproducible and to achieve this, it is essential to control the virulence of the bacteria and the quantity of bacterial inoculate employed. Our model uses strains of uropathogenic *E. coli* whose virulence is tested by polymerase chain reaction for the presence or absence of a panel of genes encoding known virulence factors (toxins, adhesins, siderophores and capsules). And, with regard to the bacteriological analysis, samples are cultured on Muller–Hinton solution, then tissues are crushed using a sterile scalpel and pots containing the meshes are incubated for 18 h at 37°C.

Rats have already been used in the past to test for the infection of prostheses, but excision was in all cases early, on day 7 [9, 22]. We chose late explantation 30 days after surgery, and this is for two reasons. First, we considered it important to wait until after the immediate inflammatory reaction, and, second, postoperative complications due to meshes implanted by the vaginal route seldom occur soon after surgery. We chose to inoculate animals with *E. coli* as this bacterium is often implicated in urogenital infections and often colonizes the vaginal mucosa. It may become offensive, acquiring pathogenic islets that include genes coding for a variety of virulence factors (toxins, siderophores and capsules). In our first experiment, the persistent infection of all meshes on day 30 with the same *E. coli* validated our decision to use this bacterium. Yet, culture swabs were polymicrobial, with mainly commensal microorganisms (*Staphylococcus epidermidis*, *Corynebacteriae*) or colonizing saprophytes (*S. aureus*). *P. mirabilis* was the only pathogenic bacteria, and may have been the consequence of surgical contamination. We chose model parameters in such a manner to result in the slightest possible infection of the mesh for infection in clinical practice probably arises from involuntary contamination with a small number of microorganisms. In confirmation of this, when meshes are removed because of clinical complications (erosion, infection) and cultured, only a low bacterial density is usually found. Our minimal infection of the mesh therefore more closely matches clinical conditions.

What have we learned from basic science?

A subclinical mesh infection, acquired during the initial implantation, may result in wound separation with subsequent mesh exposure [23].

If vaginal erosion is detected, it raises the question of whether mesh colonization is a risk factor for erosion, or whether erosion exposes the mesh to vaginal bacteria that then colonize it [13].

In a recent study, we put forward the hypothesis that mesh infection stemming from bacterial contamination during the implantation phase is an independent risk factor for shrinkage [24]. A low concentration of bacterial cells (10^6 CFU) was injected onto the mesh intraoperatively in order to mimic subclinical bacterial contamination. A significant correlation was observed between infection and shrinkage.

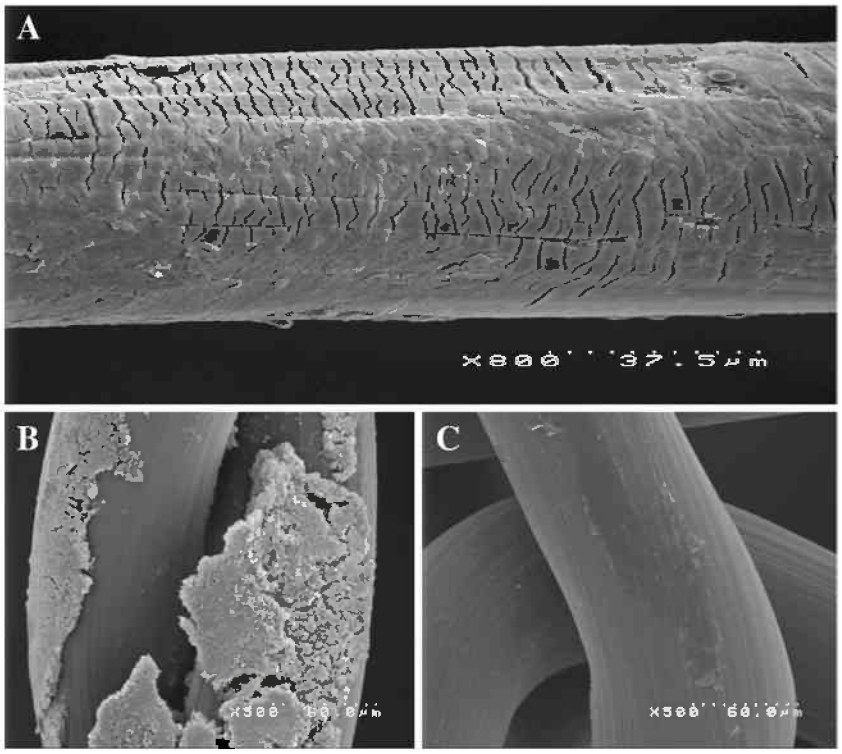

Fig. 1 Scanning electron microscopy of low-weight, macroporous, monofilament knitted polypropylene mesh extracted after 30 days with infection by *E. coli* in an incisional abdominal hernia model in Wistar rats. The explanted infected mesh shows transverse cracks (**a**). After washing with DMSO (**b**) and ultrasonic shock (**c**), it appears marked modifications in mesh surface corresponding to the biofilm (**a**), and after biofilm removal, no polymer degradation was seen any more (**c**)

Using the same model of mesh infection, we also experimentally tested Clave's conclusion [15] regarding a correlation between infection and polypropylene "degradation". Polypropylene meshes were implanted in the incisional abdominal hernia model in Wistar rats and inoculated with 10^6 CFU of *E. coli*, as described previously [24]. After 30 days the meshes were explanted and washed with dimethyl sulfoxide (DMSO) and ultrasonic shock, then examined by environmental scanning electron microscope (ESEM). At the same time, polypropylene meshes were inoculated in vitro with the same isolate of *E. coli*, then explanted after 2–15 days and washed with the same process. In these studies we also observed signs of superficial degradation and transverse cracks (Figs. 1 and 2), but this appeared to concern only the biofilm, with no effect on the implant thread itself (unpublished data).

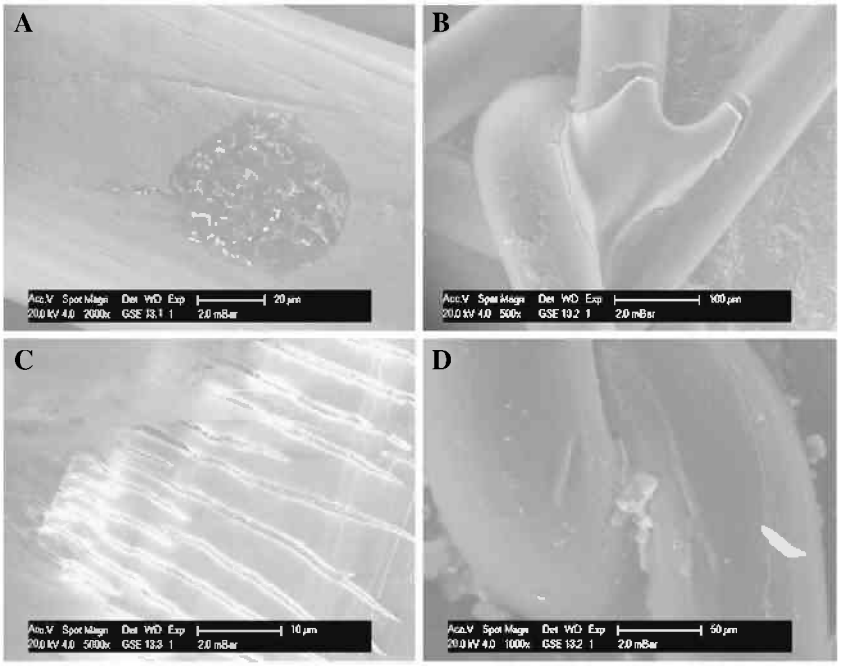

Fig. 2 ESEM of in vitro infection of low-weight polypropylene macroporous knitted mesh extracted from a bacterial culture medium infected by *E. coli* after 2 (**a**), 5 (**b**) and 15 days (**c**). **a** Beginning of biofilm formation. **b** Cracks in the biofilm at mesh interstices. **c** Transverse cracks in the biofilm. **d** Non-degraded polymer thread after washing out the biofilm

Perspectives

Although the short- to medium-term risk of infection and subsequent erosion, shrinkage or repeat operation for partial or complete mesh removal is now better understood, knowledge is still lacking for the long term. Recently, two case reports, one concerning an enterocutaneous fistula 14 years after prosthetic mesh repair of a ventral incisional hernia [25] and the other a suprapubic vaginocutaneous fistula 18 years after a bladder-neck suspension [26], were interviewed if pelvic reconstructive surgery using polypropylene mesh by the vaginal route is a lifelong risk.

Tissue ingrowth around synthetic implants is a complex phenomenon, indissociable from the inflammatory reaction. An immunochemical analysis of infected implanted mesh would be of great interest, with a particular focus on transforming growth factor (TGF)-beta1 which is a determinant of foreign body reaction to alloplastic materials in rat fibroblast cultures [27]. This type of study should be able to differentiate between the respective responsibilities in mesh shrinkage of bacterial contamination and non-infectious foreign body reactions. Should the hypothesis be confirmed, the use of antibacterial products on synthetic implants would be greatly beneficial in women.

Antibiotics may be used protectively during the initially vulnerable period before the surface is stabilized, when random colonization by bacteria might occur [4]. Parallel to the potential advantages of coating with antibiotics, silver coated-mesh has been shown to reduce bacterial colonization around the mesh [28].

Biomaterial surfaces must be modified to improve compatibility and tissue integration, and resist microbial colonization in the "race for the surface" [4]. Modifications of the mesh surface, such as brush coating, have been shown to be effective in reducing the development of a less mature and less organized bacterial biofilm, resulting in decreased bacterial contamination of the implant [3]. With no antibiotic or antiseptic on the mesh, this simple physicochemical modification could give prophylactic intravenous antibiotics a better chance of killing any bacteria that have adhered to a brush-coated implant surface during surgery, and this prior to the formation of a more mature and thus more resistant biofilm.

Conclusion

Bacterial colonization following mesh-augmented pelvic floor reconstructive surgery for pelvic organ prolapse is probably an underestimated consideration. Prolonged inflammatory response and chronic infection could be two different mechanisms, which may coexist, explaining local complications such as painful shrinkage. However, the exact role of infection must be explored by further experimental and clinical studies.

Conflicts of interest None.

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